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STAT

EFFECTS OF IONIZING RADIATION ON THE NERVOUS SYSTEM OF ANIMALS

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The discovery that ionizing radiation exerts an effect on biological objects has imposed on science the task of studying the modifications which take place in the organism under the effect of this radiation and of explaining the mechanism of their development. A great number of investigations has been carried out in this field.

During recent years Soviet scientists have accumulated a considerable amount of experimental data which characterize the reactions of tissues and organs in response to general irradiation of the animal. These changes are determined by the participation in them of the nervous system and of the neuroendocrine and some other mechanisms. The local or primary changes which arise as a result of the immediate effect of ionizing radiation on tissues and organs were found to take place side by side with physiological effects produced by nervous and humoral action.

Of particular importance are the effects exerted by the nervous system. Their character is determined by the changes of the functional state of this system which develop when the animal has been irradiated.

Of considerable importance for the formation of our ideas on the action of ionizing radiation were investigations carried out by the method of conditioned reflexes. Applied originally for the evaluation of changes taking place in the higher divisions of the central nervous system after exposure to the action of ionizing radiation, this method was used by M. I. Nemenov and since then has been applied by many Soviet investigators. According to Nemenov's data, an increase in the intensity of conditioned reflexes followed by lowering of this intensity takes place as a rule after the head of an animal has been irradiated with 2,500 - 3,500 roentgen.

Recently N. N. Livshits has found that upon general irradiation of an animal there may take place, depending on the dose of radiation, either a weakening of the process of internal inhibition alone or reduction of the intensities of both inhibition and excitation.

When the interrelationship between the intensity of the conditioned irritants and the magnitude of the conditioned reactions corresponding to them is investigated after irradiation, relationships which deviate from the normal are often observed. One finds that in response to a strong irritation a weak conditioned reaction takes place or a weak irritation is followed by a strong reaction. The condition that arises is regarded as a transitory state between excitation and inhibition. Such conditions have been designated as phasic conditions or states at Pavlov's laboratories.

The modifications of the processes of excitation and inhibition which have been mentioned above and also the development of phasic states indicate that significant changes in the cortical dynamics may occur following irradiation. Supplementing research on the modification of the cortical dynamics arising as a result of ionizing radiation in dogs, a number of authors has investigated the conditioned reflex activity of rats. At P. D. Gorizontov's laboratory, A. Grafov

STAT

in investigations dealing with the motor conditioned reflexes of rats which have received a dose of radiation amounting to 600 roentgen, discovered that three periods of successive changes follow irradiation.

In the first of these periods, which begins within 20-40 minutes after irradiation, there is a sharp weakening of the process of internal inhibition. When phasic states (the narcotic and equalizing phases) develop, there is a transition to the second period of changes involving suppression of cortical activity which proceeds up to a complete disappearance of conditioned reflexes. The third period is characterized by a restoration of conditioned reflex activity. However, the animals which survive may retain for a long time an instability of the conditioned reflex reactions and a reduction of the mobility of the nervous processes.

Electroencephalographic data have served as an important supplement to the results of investigations of the functional condition of higher divisions of the central nervous system with the aid of the conditioned reflex method. The first indications to the effect that changes in the electrical activity of the brain take place under the effect of irradiation were obtained in experiments with radon by M. N. Livanov. The investigations carried out by Livanov demonstrated that as a result of the action of mixed beta and gamma radiation, there is a distinct weakening of the bioelectric activity.

Subsequently to this, beginning with the second day after irradiation, restoration of spontaneous electrical activity takes place. However, the reaction to irritants remains disturbed: the excitability is sometimes increased and sometimes lowered.

Electrophysiological investigations carried out in combination with pharmacological experiments will enable us to acquire a still better knowledge of the nature of changes which occur in the higher divisions of the central nervous system. Thus, when the electrical activity of the cerebral cortex was measured in sick persons who had been subjected to X-ray irradiation for therapeutic purposes, it was established that the administration of small doses of caffeine prior to irradiation increases the electrical activity of the cortex. After irradiation, administration of identical doses of the drug upon exposure of the subjects to the action of light stimuli of ordinary intensity often brings about a severe and profound depression of electrical activity. This can be explained by the assumption that irradiation lowers the limit of the working capacity of cortical cells. As has been established by the work of Pavlov's school, caffeine reinforces the process of excitation. Against the background of a lowered limit of the working capacity of cortical cells, this reinforcement proves to be excessive, so that the cortical cells are unable to respond with excitation to the action of the light stimulus. Cortical cells which operate beyond the limit of their working capacity respond with the reaction of inhibition under the circumstances.

Of great interest is the utilization of a new method proposed by M. N. Livanov and V. M. Anan'ev for the evaluation of changes in the higher divisions of the central nervous system which arise after the organism has been subjected to the action of ionizing radiation. This method makes it possible to carry out a spacial study of the principal nervous processes taking place in the cerebral cortex because a great number of points within the cortex is included in the amplifier system. By using a gradual amplification procedure ["the commutational principle"] for including these points into the circuit, we may observe the complex dynamics of the cortical mosaic in animals and human beings. With the aid of this method, changes in the spacial dynamics after a single massive irradiation with X-rays were investigated.

It has been shown that the shifts brought about by radiation affect in a uniform manner the whole cerebral cortex. During the first hours after exposure to radiant energy, the cortical mosaic becomes more strongly accentuated, i. e., is reinforced. Following this, it weakens for a long period of time (several

STAT

days or a period longer than that). Later, an unstable condition is observed and there is a tendency towards the restoration of the initial dynamics of cortical activity.

In animals which have been exposed to irradiation with massive total doses, the dynamics of the nerve processes in the cerebral cortex deviate often sharply from the normal for a long period of time (2 months). One then observes in the cortex reinforcement of processes of inhibition and distinct changes in the spacial relationships between the processes of excitation and inhibition.

The data outlined above force us to revise the assumption prevalent hitherto according to which the central nervous system is resistant to the effects of radiation.

The physiological data indicating changes in the functional condition of the central nervous system under the effect of radiation to which an animal organism is subjected are in agreement with the results of morphological observations.

B. N. Mogil'nitskiy, L. D. Podlyashuk, D. G. Shefer, T. S. Kupalov, R. S. Liman, and others describe changes in the elements of the central nervous system which often progress to a considerable degree.

Lately, a number of investigations has been carried out in this field in which histological and histochemical methods were combined. V. B. Portugalov and his collaborators observed that at the height of the development of the symptoms of radiation sickness there is an increase in the activity of alkaline phosphatase in the Schwann sheathes of the peripheral nerves. Very soon after irradiation there are changes in the sensory neurons of the spinal cord ganglia, receptors, and sympathetic ganglia.

One of the principal facts discovered in the morphological investigation of the central nervous system after it has been subjected to the action of ionizing radiation is the uneven degree of development of these changes. In the cerebral cortex, mesencephalon (red nuclei), the nuclei of the pons varolii, and the spinal cord they are less pronounced than in the region below the bulges, the vicinity of the sylvian duct, some elements of the corpus quadrigeminum, and some nuclei of the medulla oblongata.

What is the origin of the changes in the functional condition of the central nervous system which have been described and which arise after the animal has been exposed to ionizing radiation?

In this respect, the possibility that a number of mechanisms is effective must be recognized. First of all, it must be assumed that there is a direct action of the ionizing radiation of the central nervous system. There are no reasons to deny this possibility, because the ionizing effect must be exerted on the brain tissue just as it is exerted on any other tissue. In the nervous system one observes a biochemical effect produced by the ionizing action which is also typical of other tissues, namely a change in the nucleic metabolism. At the height of the development of symptoms arising subsequently to the action of ionizing radiation, occurrence of changes in the content of ribonucleic acid in the nervous system of the cat can be established by histochemical methods.

These changes are not the same in all cells: in some cells the content of ribonucleic acid increases, in others it drops, while in still others it remains unchanged. In the spinal cord and the cells of the spinal ganglia there is most frequently a reduction of the ribonucleic acid content. In the anterior cornua of the spinal cord and in the cerebral cortex, the content of this acid is usually increased.

STAT

One of the causes of the disturbance of the functional condition of the central nervous system may be disturbances of circulation as well as changes in the permeability of the brain's capillaries and disturbances affecting the condition of argyrophilic fibers in the vascular walls and also in the perivascular spaces. An increased level of glycolysis in brain tissues after irradiation has also been observed. Circulatory disturbances in the brain are combined with a disturbance in the utilization of oxygen by brain tissue.

The most important cause of the disturbance noted is an interference with the transmission of impulses from the periphery to the central nervous system and, what is particularly important, into the cerebral cortex. Furthermore, one must assume the possibility of the appearance of unusual irritants in the pathologically changed tissues and organs.

Equally explicit are the data pertaining to changes in the functioning of the receptors of internal organs after irradiation. The fact that disturbances of this type take place is confirmed in particular by a reinforcement of the bioelectrical activity of the sinocarotid nerve in response to an increase of pressure in the isolated sinus, reinforcement of the interoreceptor reflexes on extension of the rectum, and changes in the reflex reactions resulting from the action of chemical irritants on the receptors of blood vessels.

Work which characterizes changes in the condition of the interoreceptors after action of ionizing radiation on the animal organism is of great importance. Investigations by K. M. Bykov and members of his group have shown that unusual impulses arising at interoreceptors may be the cause of disturbances in the functioning of the central nervous system. A direct proof of the importance of reflex irritations in the development of disturbances of the central nervous system has been furnished in experiments conducted by L. I. Lomonos, who investigated the conditioned reflexes of dogs which had been irradiated with X-rays in the process of projecting a picture of their head upon a screen. Lowering of the intensity of food reflexes and increase in the intensity of defensive conditioned reflexes was noted in these experiments.

An important question arises in regard to the significance of the changes in the functional condition of the central nervous system described above among reactions of the organism brought about by ionizing radiation. Prior to answering this question it is necessary to discuss another, very important question as to what formations of the central nervous system are afflicted to the greatest degree. As has been stated above, morphological changes within the brain stem proved to be more pronounced than changes in other divisions of the central nervous system. Particularly great are the disturbances in the region of the higher vegetative centers, i. e., the region below the bulges and in the medulla oblongata.

On the basis of electrophysiological investigations, M. N. Livanov reached the conclusion that the most important functional changes in irradiated animals are observed in the subcortical formations. By comparing the changes of electrical activity in the cortex with those in the subcortex taking place in animals after general irradiation, he succeeded in establishing that the disturbances in the bioelectrical activity of the subcortex which arise after irradiation continuously increase and even increase when there is a temporary to normal of bioelectric phenomena in the cortex. The lowering of thresholds in the subcortex continues to increase in magnitude until the death of the animal. In individual regions of the subcortex, foci of a parabiologic state arise which block the propagation of an excitation. Gradually, in a constantly accelerating rhythm, sharp angular waves appear in the subcortical region, and these waves then spread into the cerebral cortex.

Very significant is the fact that subsequently to the action of ionizing radiation on the animal organism, changes arise not only in centers of the

STAT

vegetative nervous system but also in the peripheral formations of this system. D. V. Portugalov has shown that after irradiation of an animal, the staining properties of nerve cells in the sympathetic ganglia change within one day. Gaps form in the body of the cells and individual vacuoles are formed; there is also an increased capacity of the cells to be stained with silver salts. Taken by themselves, these changes are minor and do not indicate any severe modifications of the structure of the nerve cells. However, they progress steadily during the period following the irradiation. Towards the 3rd day, the destructive changes in the nerve cells become expressed to a noticeable degree; at the end of a week these destructive changes predominate, spreading to a great number of neurons.

In answering the question as to which divisions of the central nervous system are modified in the most severe manner as far as their functional condition is concerned, it must be kept in mind that the most prominent disturbances occur in the region of subcortical formations. However, it should not be concluded from this that disturbances of the functions of the cerebral cortex are negligible. They may apparently arise independently of the functional state of the subcortex. This is shown by the data of N. N. Livshits, who observed disturbances in the conditioned reflex activity of animals in the absence of any changes in the nutritional unconditioned reflexes. Primary disturbances of this type in the functioning of the cerebral cortex not only bring about changes in the higher nervous activity and the conduct of the animal, but also exert in turn a definite influence on the subcortex.

Summarizing all the facts mentioned above, one may draw the conclusion that severe functional changes take place in the nervous system when an animal is exposed to the general action of ionizing radiation. As the experiments have shown, this circumstance forms one of the most important factors that induces changes in the character and force of the local disturbances arising under the effect of ionizing radiation. As a result the local reaction to ionizing radiation is modified substantially: it may be reinforced in its manifestations or restricted. The changes which have taken place are compensated. For this reason the reaction to ionizing radiation which is observed in higher animals substantially differs from phenomena that are known to occur in isolated tissues and organs or are exhibited by relatively primitive living organisms.

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